1 404 868

PATENT SPECIFICATION

(11) 1 404 868

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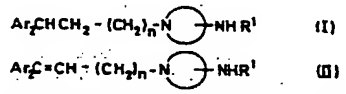
(19)

(54) PYRIDINE, TETRAHYDROPYRIDINE AND PIPERIDINE DERIVATIVES

(71) We, JOHN WYETH & BROTHER LIMITED, of Huntercombe Lane South, Taplow, Maidenhead, Berkshire, a British Company do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

The invention relates to heterocyclic compounds with useful pharmacological properties.

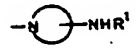
According to the present invention there is provided compounds of the formula (I) or (II)



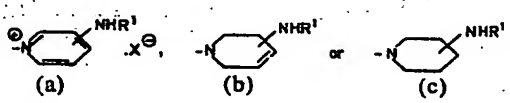
(I)

(II)

wherein Ar represents a substituted or unsubstituted phenyl radical,



represents a ring system of the general formula



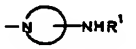
(a) (b) (c)

wherein R^1 represents hydrogen or the group COR where R represents a substituted or unsubstituted phenyl radical, a cycloalkyl radical containing from 5 to 7 carbon atoms, or a lower alkyl radical X is an anion and n is an integer of from 1 to 4, and the acid addition salts of those compounds which contain a ring system of formula (b) or (C).

Preferably —NHR^1 is in the 4-position and X is a halogen atom.

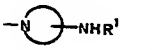
Examples of acid addition salts are those formed from inorganic and organic acids in particular pharmaceutically acceptable acid addition salts such as the sulphate, hydrochloride, hydrobromide, hydro-iodide, nitrate, phosphate, sulphonate (such as the methane-sulphonate and *p*-toluene-sulphonate), acetate, maleate, fumarate, tartrate and formate.

The compounds of formula I and II, wherein

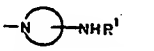


is a ring system of formula (b) or (c) where R^1 is COR where R is a substituted or unsubstituted phenyl radical or a cycloalkyl radical possess pharmacological activity for example hypotensive or antidysrhythmic activity. Compounds of formula (II) are generally less active than the corresponding compounds of

formula I and are primarily useful as intermediates in the preparation of compounds of formula I. Compounds of formula I and II wherein.



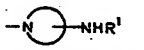
represents a ring system of formula (a) are intermediates for the corresponding compounds wherein



has the formula (b) or (c). Compounds wherein R represents lower alkyl are primarily intermediates for the corresponding compounds wherein —NHR^1 represents —NH_2. The latter compounds are also primarily intermediates for the corresponding compounds wherein —NHR^1 represents —NHCOR where R is a substituted or unsubstituted phenyl radical or a cycloalkyl radical.

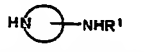
Examples or R and Ar are unsubstituted phenyl or phenyl substituted by one or more groups, which may be the same or different selected from halogen (for example fluorine, chlorine or bromine), lower alkyl (for example methyl, ethyl, propyl, or butyl), lower alkoxy (for example methoxy, ethoxy, propoxy or butoxy), nitro, amino (including alkyl or dialkyl substituted amino groups) in particular dialkylamino (for example dimethylamino or diethylamino), acylamino in particular alkanoylamino [for example acetylamino (acetamido)], hydroxyl, carboxyl, lower alkoxycarbonyl, alkylenedioxy (for example methylenedioxy), trihaloalkyl (for example trifluoromethyl), mercapto, methylthio, methylsulphonyl, phenyl and phenyl substituted by one or more of those substituents mentioned immediately above in connection with the substituted phenyl group R or Ar. Further examples of R are cyclopentyl, cyclohexyl or cycloheptyl, and methyl, ethyl, propyl and butyl.

The invention includes processes for preparing compounds of formula I and II. The preferred method for preparing compounds of formula I wherein



has formula (c) comprises catalytically hydrogenating a compound of formula II. The hydrogenation may be carried out with hydrogen in the presence of a hydrogenation catalyst such as a palladium or platinum catalyst. A suitable catalyst is palladium on carbon. If the compound of formula II has a pyridine ring of formula (a) or a tetrahydropyridine ring of formula (b) the hydrogenation should be carried out so as to reduce both the ethylenic bond and the ring system.

The preferred method of preparing a compound of formula II wherein R^1 is the —COR group is by reacting a compound of formula III



wherein R is as defined above with a compound of formula (IV)

$$Ar_2.C{=}CH{-}(CH_2)_n{-}Y \qquad (IV)$$

wherein Ar, and n are as defined above and Y is a halogen atom e.g. chlorine or bromine or an equivalent replaceable atom or radical, for example an organic sulphonyl radical such as a tosyl radical.

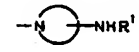
Compounds of formula I wherein R^1 is the —COR group may also be prepared by reacting a compound of formula (III) as defined above with the compound of formula (V).

$$Ar_2CHCH_2(CH_2)_n{-}Y \qquad (V)$$

where Ar, n and Y are as defined in connection with formula (IV)

Many suitable compounds of formula III are described in the complete specification filed in pursuance of our cognate applications 42090/70 and 34376/71 (now Patent No. 1,345,872).

A further method which may be used in the preparation of compounds of formula I or II in which



represents a ring system of formula (b) or (c) and R is the group —COR comprises reacting a compound of formula (VI) or (VII)

$$Ar_2C{=}CH(CH_2)_n{-}OH \quad (VI)$$

or

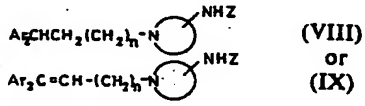
$$Ar_2CHCH_2(CH_2)_n{-}OH \quad (VII)$$

wherein Ar and n are as defined above with a compound of formula (III) as defined above.

The reaction is preferably carried out in the presence of a catalyst, for example Raney Nickel. An organic solvent, which is inert under the reaction conditions, is usually used for example xylene, toluene or benzene. Preferably the reaction is carried out by heating the reactants under reflux in a water-immiscible organic solvent, for example xylene, and removing the water formed during the reaction by azeotropic distillation. If necessary, reactive substituent groups can be blocked during a reaction and released later.

A general method of preparation of compounds of formula (I) and (II) in which R^1 is the —COR group, comprises reacting a compound of formula (I) or (II) in which R^1 is a hydrogen atom, with a reactive derivative of an acid of general formula R.COOH (where R is substituted or unsubstituted phenyl, cycloalkyl or lower alkyl). As a reactive derivative of the acid of formula R.COOH used in the process described above, we have found it preferable usually to use a halide (for example the chloride or bromide) or an anhydride. Other examples of reactive derivatives of the acid R.COOH which may be used are the acid azide, mixed anhydrides and active esters. Futhermore, the compounds of formula (I) or (II) in which R^1 is the —COR group may also be prepared by treating a compound of formula (I) or (II) in which R^1 is a hydrogen atom with the acid R.COOH in the presence of a known condensing agent (for example, a carbodiimide), or by first activating the amino function (for example, by forming the phosphazo derivative) and then reacting with the acid R.COOH. In connection with the introduction of the —COR group into a compound of formula (I) or (II) in which R^1 is a hydrogen atom, reference may be made to "Chemistry of the Amino Acids" by Greenstein and Winitz (John Wiley & Sons. Inc., Publishers, 1961) at pages 782—883 and 943—1108.

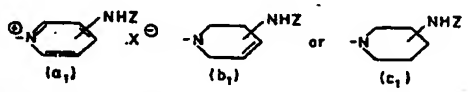
When it is desired to prepare a compound of general formula (I) or (II) wherein R^1 is a hydrogen atom a corresponding compound of formula



(VIII) or (IX)

(wherein Ar and n have the meanings defined in connection with formula (I) and (II),

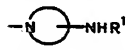
represents a ring system of formula



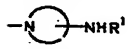
and Z is a protecting group known in the art for the protection of the amino function, is subjected to hydrolysis, hydrogenolysis or some other reaction known in the art for the removal of the protecting group Z. As examples of Z, mention is made of those wherein Z is the group —COR and R is lower alkyl, loweralkoxy and aryloxy (particularly methyl, ethoxy and phenoxy respectively). Other examples of Z are benzyl, *p*-toluene-sulphonyl, phthalyl, trityl, trifluoroacetyl,

formyl and benzylsulphonyl. Reference may be made to the review of protecting groups in Advances in Organic Chemistry, *3*, 191—294 (Interscience Publishers 1963), and also to Chemistry of the Amino Acids by Greenstein and Winitz, Vol. 2, pages 885—924 (John Wiley & Sons Inc., 1961). The compounds of general formula (VIII) or (IX) can be prepared by methods analogous to those described in Specification No. 1,345,872. Convenient starting materials for compounds of formula I and II in which R^1 is hydrogen are the corresponding compounds of formula I and II in which R^1 represents COR where R is a lower alkyl group and these may be prepared by the methods outlined above.

Once a compound of general formula (I) or (II) has been prepared, then if necessary one or more substituents in the molecule may be converted to another substituent each within its own meanings specified in connection with formula (I) or (II). If a compound if produced in which



represents the pyridinium ring system of formula (a), this may be selectively reduced to one of the other ring systems of lower oxidation state. For example, reduction with an alkali metal borohydride gives the tetrahydropyridine ring system of formula (b). On the other hand, catalytic hydrogenation, for example, in the presence of Raney Nickel or a platinum catalyst, or careful reduction with a hydride transfer agent (such as lithium aluminium hydride) gives rise to the piperidine ring system of formula (c). However catalytic hydrogenation will also reduce the ethylenic bond in compounds of formula (II). Similarly if a compound of formula (I) or (II) is prepared in which



represents the tetrahydropyridine ring system of formula (b), this may also be reduced to the piperidine ring system of formula (c).

When a compound of formula (I) or (II) is produced wherein the radical Ar has one or more methoxy substituents, hydrolysis to the corresponding hydroxyl compound may be brought about in known manner. Futhermore, if the radical Ar has a nitro substituent this may be reduced in known manner to the corresponding amino compound which in turn may be further acylated or alkylated.

When a compound of formula (I) or (II) is produced wherein the radical Ar has one or more methoxy substituents. hydrolysis to the corresponding hydroxyl compound may be brough about in known manner. Futhermore, if the radical Ar has a nitro substituent this may reduced in known manner to the corresponding amino compound which is turn may be further acylated or alkylated.

The invention includes pharmaceutical compositions containing as active ingredient an active compound of formula (I) or (II) as hereinbefore defined, which may be micronised. In addition to the active ingredient, said compositions also contain a non-toxic carrier. Any suitable carrier known in the art can be used to prepare the pharmaceutical compositions. In such a composition, the carrier may be a solid, liquid or mixture of a solid and a liquid. Solid form compositions include powders, tablets and capsules. A solid carrier can be one or more substances which may also act as flavouring agents, libricants, solubilisers, suspending agents, binders, or tablet-disintegrating agents; it can also be an encapsulating material. In powders the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets the active ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from 5 to 99, preferably 10—80% of the active ingredient. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low melting wax, and cocoa butter. The term "composition" is intended to include the formulation of an active ingredient with encapsulating material as carrier to give a capsule in which the active ingredient (with or without other carriers) is surrounded by carrier, which is thus in association with it. Similarly cachets are included.

Sterile liquid form compositions include sterile solutions, suspensions, emulsions, syrups and elixirs. The active ingredient can be dissolved or suspended

in a pharmaceutically acceptable sterile liquid carrier, such as a sterile water, sterile organic solvent or a mixture of both. Preferably a liquid carrier is one suitable for parenteral injection. Where the active ingredient is sufficiently soluble it can be dissolved in normal saline as a carrier; if it is too insoluble for this it can often be dissolved in a suitable organic solvent, for instance aqueous propylene glycol or polyethylene glycol solutions. Aqueous propylene glycol containing from 10 to 75% of the glycol by weight is generally suitable. In other instances compositions can be made by dispersing the finely-divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution, or in a suitable oil, for instance arachis oil. Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilised by intramuscular, intraperitoneal or subcutaneous injection. In many instances a compound is orally active and can be administered orally either in liquid or solid composition form.

Preferably the pharmaceutical composition is in unit dosage form. In such form, the composition is sub-divided in unit doses containing appropriate quantities of the active ingredient; the unit dosage form can be a packaged composition, the package containging specific quantities of compositions, for example packeted powders or vials or ampoules. The unit dosage form can be a capsule, cachet or tablet itself, or it can be the appropriate number of any of these in package form. The quantity of active ingredient in a unit dose of composition may be varied or adjusted from 5 mg. or less to 500 or more, according to the particular need and the activity of the active ingredient. The invention also includes the compounds in the absence of carrier where the compounds are in unit dosage form.

The following non-limiting Examples illustrate the invention:

Example 1.

4-(4-Benzamidopiperid-1-yl-1,1-(di-*p*-fluorophenyl) but-1-ene

4-Benzamidopiperidine (2.687 g.) was alkylated with 1,1-di-*p*-fluorophenyl)4-chlorobut-1-ene (3.784 g.) by heating the reagents together with finely ground potassium carbonate (JLA) on a steam bath for one hour. The solid obtained was stirred in water at 60° for one hour and the title compound filtered off, washed well with water and ether to give the free base. This was dissolved in hot absolute ethanol and the solution acidified with ethanolic hydrogen chloride, then cooled to give the title product as the hydrochloride, hemihydrate in 28% yield (1.821 g.) m.p. 272.7°C.

$C_{28}H_{24}F_2O.HCl.\frac{1}{2}H_2O$ requires C, 68.34; H, 6.15; N, 5.69. Found C, 68.29; H, 6.19; N, 5.17%.

The product exhibits hypotensive activity and is an intermediate for the compound of the next example.

Example 2.

4-(4-Benzamidopiperid-1-yl)-1,1-(di-*p*-fluorophenyl) butane

4-(4-Benzamidopiperid-1-yl)-1,1-(di-*p*-fluorophenyl)but-1-ene, hydrochloride (885 mg.) was hydrogenated using 10% palladium charcoal (1.0 g.) at 50 p.s.i. and 50° in methanol (120 ml.) containing a few drops of concentrated hydrochloric acid for 24 hours. The catalyst was filtered off and the filtrate was evaporated to give a residue which gave hydrochloride of the title compound (277 mg., 31.2%) m.p. 256.8°, on treatment with ethanolic hydrogen chloride and ether. $C_{28}H_{30}F_2N_2O.HCl$ requires C, 69.35; H, 6.44; N, 5.78. Found: C, 69.34; H, 6.79; N, 5.95%.

The product exhibited hypotensive activity in a standard test procedure and caused pronounced decrease in cardiac contractile force in rats and cats in a test procedure.

Example 3.

4-(4-Benzamidopiperid-1-yl)-1,1-diphenylbut-1-ene

Using the procedure of Example 1 over a period of 20 hours, 4-benzamidopiperidine (7.473 g.) was alkyiated with 1,1-diphenyl-4-chlorobut-1-ene (8.879 g.). The title compound was filtered of after addition of water and ether to the reaction mixture and a further crop was obtained from the ether washings. Conversion of the combined product to the hydrochloride using ethanolic hydrogen chloride gave 6.308 g. (38.2%), m.p. 220—230°(dec.). $C_{28}H_{30}N_2O.HCl.1/4H_2O$ requires C, 74.46; H, 7.03; N, 6.20. Found: C, 74.77; H, 7.26: N, 6.14%.

The product exhibited hypotensive activity in a standard test procedure and is an intermediate for the compound of the next example.

Example 4.

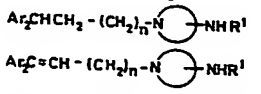
4-(4-Benzamidopiperid-1-yl)-1,1-diphenyl butane

Using the procedure of Example 2 4-(4-Benzamidopiperid-1-yl)-1,1-diphenylbut-1-ene (4.105 g., 0.01 mole) was reduced to the title compound using 500 mg. of 10% palladium-charcoal. The hydrochloride of the product was obtained using the method of Example 1 in 62.4% yield (2.800 g.) m.p. 269.2°. $C_{28}H_{32}N_2O.HCl$ requires C, 74.90; H, 7.41; N, 6.24. Found: C, 74.55; H, 7.47; N, 6.15%.

The product exhibited hypotensive activity in a standard test procedure.

WHAT WE CLAIM IS:—

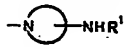
1. A compound of the formula (I) or (II)



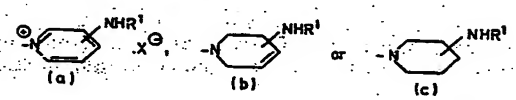
(I)

(II)

wherein Ar represents a substituted or unsubstituted phenyl radical,



represents a ring system of the general formula



wherein R^1 represents hydrogen or the group COR where R represents a substituted or unsubstituted phenyl radical, a cycloalkyl radical containing from 5 to 7 carbon atoms, or a lower alkyl radical, X is an anion and n is an integer of from 1 to 4, or an acid addition salt of a compound of formula I or II which contains a ring system of formula (b) or (c).

2. A compound as claimed in claim 1, wherein the radical $—NHR^1$ is in the 4-position.

3. A compound as claimed in claim 1 or claim 2 wherein n is 2.

4. A compound as claimed in any one of claims 1 to 4, wherein Ar is a holophenyl radical.

5. A compound as claimed in claim 4 wherein Ar is a fluorophenyl radical.

6. A compound as claimed in claim 5 wherein Ar is a *p*-fluorophenyl radical.

7. 4-(4-Benzamidopiperid-1-yl)-1,1-(di-*p*-fluorophenyl)but-1-ene or an acid addition salt thereof.

8. 4-(4-Benzamido-1-yl)-1,1-(di-p-fluorophenyl)butane or an acid salt thereof.

9. 4-(4-Benzamidopiperid-1-yl)-1,1-diphenylbut-1-ene or an acid addition salt thereof.

10. 4(4-Benzamidopiperid-1-yl)-1,1-diphenyl butane or an acid addition salt thereof.

11. A hydrochloride of a compound as claimed in any one of claims 1 to 10.

12. A method for preparing a compound of formula I as claimed in any of claims 1 to 6, 8 or 10 which method comprises catalytically hydrogenating a corresponding compound of formula II.

13. A method as claimed in claim 12, wherein the hydrogenation is carried out with hydrogen in the presence of a palladium or platinum catalyst.

14. A method as claimed in claim 13, wherein the catalyst is a palladium on carbon catalyst.

15. A method for preparing a compound of formula II as claimed in any one of claims 1 to 6, 7 or 9 wherein R^1 is the COR group, which method comprises reacting a compound of formula III

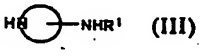
(III)

wherein R^1 is the COR group with a compound of forr IV)

$$Ar_2C{=}CH(CH_2)_2n{-}Y \qquad (IV)$$

wherein Ar, and n are as previously defined and Y is a halogen atom or an equivalent replaceable atom or radical.

16. A method for preparing a compound of formula I as claimed in any one of claims 1 to 6, 8 or 10 wherein R^1 is the group COR which method comprised reacting a compound of formula III



(III)

wherein R^1 is the group COR with a compound of formula (V)

$$Ar_2CHCH_2(CH_2)n{-}Y \qquad (V)$$

whcrein Ar and n are as previously defined and Y is a halogen atom or an equivalent replaceable atom or radical.

17. A method for preparing a compound of formula I or II as claimed in any one of claims 1 to 6, in which the group

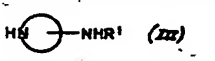
represents a ring system of formula (b) or (c) and R^1 is the group COR which method comprises reacting a compound of formula (VI) or (VII)

$$Ar_2C{=}CH(CH_2)n{-}OH \qquad (VI)$$

or

$$Ar_2CHCH_2(CH_2)n{-}OH \qquad (VII)$$

wherein Ar and n are previously defined with a compound of formula (III)



(zzz)

wherein R^1 is the group COR.

18. A method for preparing a compound of formula I or II as claimed in any one of claims 1 to 6, in which R^1 is the COR group, which method comprises reacting a corresponding compound of formula I or II wherein R^1 is hydrogen with a reactive derivative of an acid of general formula RCOOH (where R is a substituted or unsubstituted phenyl, cycloalkyl or lower alkyl radical).

19. A method for preparing a compound of formula I or II as claimed in any one of claims 1 to 6, wherein R^1 is a hydrogen atom which method comprises hydrolysing or hydrogenolysing a corresponding compound wherein R^1 is the group Z, Z being a protecting group.

20. A method as claimed in claim 19 wherein Z is the group COR wherein R is as defined in Claim 1.

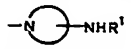
21. A method for preparing a compound of formula I or II as claimed in any one of claims 1 to 6, wherein the compound has a ring system of formula (b) or (c) which method comprises selectively reducing a compound of formula I or II which has a ring system of formula (a) or (b).

22. A method as claimed in claim 12, substantially as hereinbefore described with reference to Example 2 or 4.

23. A method as claimed in claim 15 substantially as hereinbefore described with reference to Example 1 or 3.

24. A compound whenever prepared by a method as claimed in any one of claims 12 to 23.

25. A pharmaceutical composition comprising a compound of formula I or II as claimed in any one of claims 1 to 11, wherein the ring system



has the formula (b) or (c) and R^1 is the group COR where R is a substituted or unsubstituted phenyl radical or a cycloalkyl radical, and a pharmaceutically acceptable carrier.

26. A pharmaceutical composition as claimed in claim 25, in unit dosage form.

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